Ponatinib in patients with chronic-phase chronic myeloid leukemia and the T315I mutation: 4-year results from OPTIC

Michael Deininger, MD, PhD,[1] Jane Apperley, MD,[2] Christopher Kevin Arthur, MD,[3] Charles Chuah, MD,[4] Andreas Hochhaus, Dr. med.,[5] Hugues de Lavallade, MD, PhD,[6] Jeffrey Lipton, MD, PhD,[7] Elza Lomaia, MD, PhD,[8] James McCloskey, MD,[9] Lori Maness, MD,[10] Michael Mauro, MD,[11] Beatriz Moraghi, MD,[12] Carolina Pavlovsky, MD,[13] Gianantonio Rosti, MD,[14] Philippe Rousselot, MD, PhD,[15] Maria Undurraga Sutton, MD,[16] Xiaowei Ren, PhD,[17] Alexander Vorog, MD,[17] Hagop Kantarjian, MD,[18] Jorge Cortes, MD[19]

[1]Versiti Blood Research Institute, Milwaukee, WI, USA; [2]Imperial College London, London, UK; [3]Royal North Shore Hospital, St. Leonards, Australia; [4]Singapore General Hospital, Duke-NUS Medical School, Singapore; [5]Universitätsklinikum Jena, Jena, Germany; [6]King's College Hospital NHS Foundation, London, UK; [7]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [8]Almazov National Medical Research Centre, St. Petersburg, Russia; [9]The John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ, USA; [10]University of Nebraska Medical Center, Omaha, NE, USA; [11]Memorial Sloan Kettering, New York, NY, USA; [12]Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina; [13]Fundaleu, Buenos Aires, Argentina; [14]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola (FC), Italy; [15]Centre Hospitalier de Versailles University de Versailles Saint-Quentin-en-Yvelines, Paris, France; [16]Hospital del Salvador, Santiago, Chile; [17]Takeda Development Center Americas, Inc., Lexington, MA, USA; [18]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [19]Georgia Cancer Center at Augusta University, Augusta, GA, USA

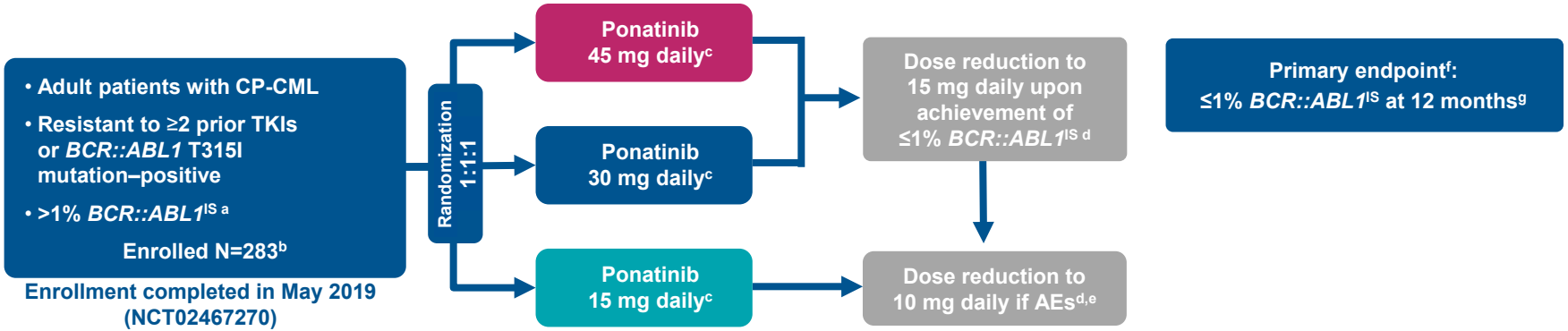
Background

- In patients with chronic-phase chronic myeloid leukemia (CP-CML) harboring the *BCR::ABL1* T315I mutation, resistance to first- and second-generation BCR::ABL1 tyrosine kinase inhibitors (TKIs) often develops, leading to poor survival outcomes[1–3]
- Ponatinib, an approved BCR::ABL1 TKI, potently inhibits native *BCR::ABL1* and all known single-resistance mutants, including T315I[2,3]
- The phase 2 OPTIC (Optimizing Ponatinib Treatment in CP-CML, NCT02467270) trial is evaluating the efficacy and safety of ponatinib using a novel response-based dosing strategy in patients with CP-CML whose disease is resistant to ≥2 TKIs or who harbor T315I[1]
- Results from the OPTIC primary analysis demonstrated robust efficacy in the overall CP-CML population and in patients with the T315I mutation[1]
- We present a post hoc analysis of the 4-year results from the OPTIC trial in patients with the T315I mutation

1. Cortes J, et al. Blood 2021;138:2042–50. 2. Cortes J, et al. N Engl J Med 2013;369:1783–96. 3. O'Hare T, et al. Cancer Cell 2009;16:401–12.

Study design

OPTIC is an ongoing multicenter randomized phase 2 trial



- This subanalysis assessed 4-year *BCR::ABL1*^{IS} response rates, progression-free survival (PFS), overall survival (OS), and safety in patients with the T315I mutation
- At the data cutoff for the 4-year analysis (May 8, 2023), median follow-up in patients with the T315I mutation was 60.6, 63.5, and 60.7 months in the 45-mg, 30-mg, and 15-mg cohorts, respectively

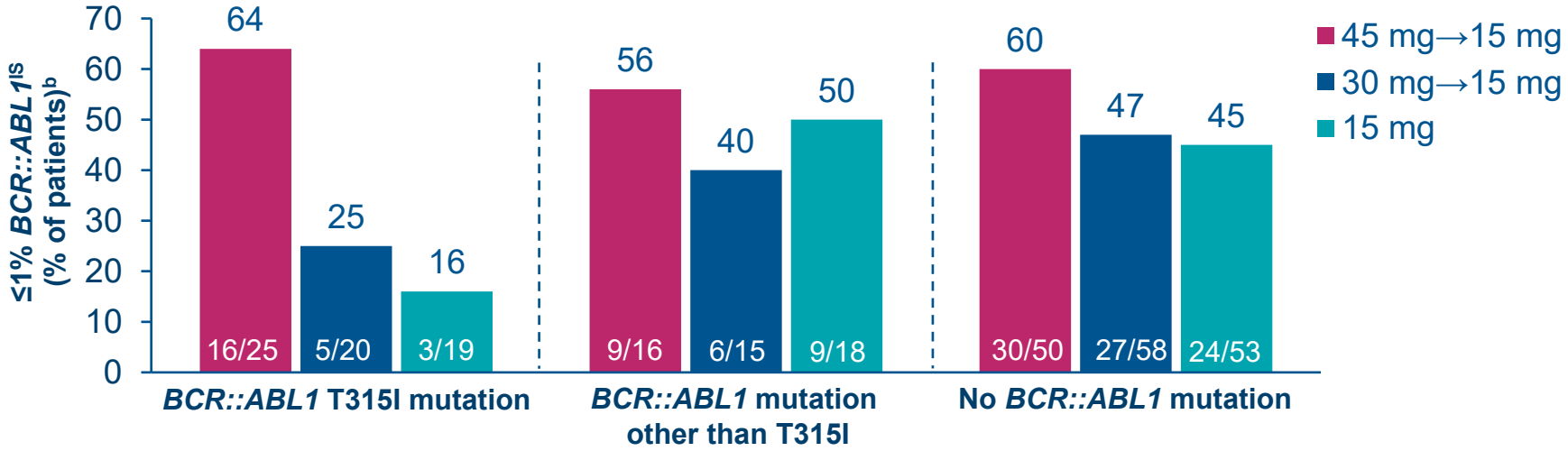
[a]As shown by quantitative real-time polymerase chain reaction; [b]99% of patients were TKI-resistant; [c]Dose reductions due to AEs were permitted; [d]Escalation to the starting dose was allowed for patients who lost their response following dose reduction; no dose escalation was allowed beyond starting dose; [e]Dose reduction below ponatinib 10 mg was not permitted during the main treatment period, but reduced dosing frequency was permitted during the treatment continuation period; [f]Key secondary endpoints: MMR rate at 12 months and 24 months and MCyR rate by 12 months, duration of MMR, and safety across the 3 doses; others include PFS, OS, and DOR in responders; [g]Statistical analysis: n≥92 patients/cohort distinguished a favorable ≤1% *BCR::ABL1*^{IS} rate of 35% from a null or uninteresting rate of 20% with a nominal 80% power and 1-sided type I error rate of 0.0083 (exact binomial test).
AE, adverse event; DOR, duration of response; MCyR, major cytogenetic response; MMR, major molecular response

Demographics and baseline disease characteristics[a]

Characteristic	Subcategory	45 mg→15 mg (n=94)	30 mg→15 mg (n=95)	15 mg (n=94)
Age, years, median (range)		46 (19–81)	51 (21–77)	49 (18–81)
Male, n (%)		50 (53)	38 (40)	53 (56)
ECOG PS 0 or 1, n (%)		93 (99)	93 (99)	94 (100)
Time since diagnosis, years, median (range)		5.5 (1–21)	5.1 (1–29)	5.7 (1–22)
Patients with CV risk factors, n (%)	Arterial hypertension	26 (28)	25 (27)	22 (23)
	Diabetes mellitus	5 (5)	3 (3)	7 (7)
	Hyperlipidemia	19 (20)	14 (15)	16 (17)
Patients with ≥2 CV risk factors, n (%)		5 (5)	4 (4)	3 (3)
Prior TKIs, n (%)	1	1 (1)	1 (1)	4 (4)
	2	43 (46)	37 (39)	42 (45)
	≥3	50 (53)	56 (60)	48 (51)
Stopped prior TKI for resistance, n (%)		92 (98)	94 (100)	94 (100)
***BCR::ABL1* mutation,[b] n (%)**	No mutation	51 (54)	58 (62)	54 (57)
	T315I mutation	25 (27)	21 (22)	21 (22)
	Other mutations	16 (17)	14 (15)	18 (19)
Best response to last prior TKI, n (%)	CHR or worse	61 (65)	55 (59)	57 (61)
	≤1% *BCR::ABL1*^{IS} or better	2 (2)	7 (7)	7 (7)

[a]Safety population. [b]Five patients (45 mg, n=2; 30 mg, n=1; 15 mg, n=2) did not have mutation testing performed at baseline.
CHR, complete hematologic response; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; PS, performance status

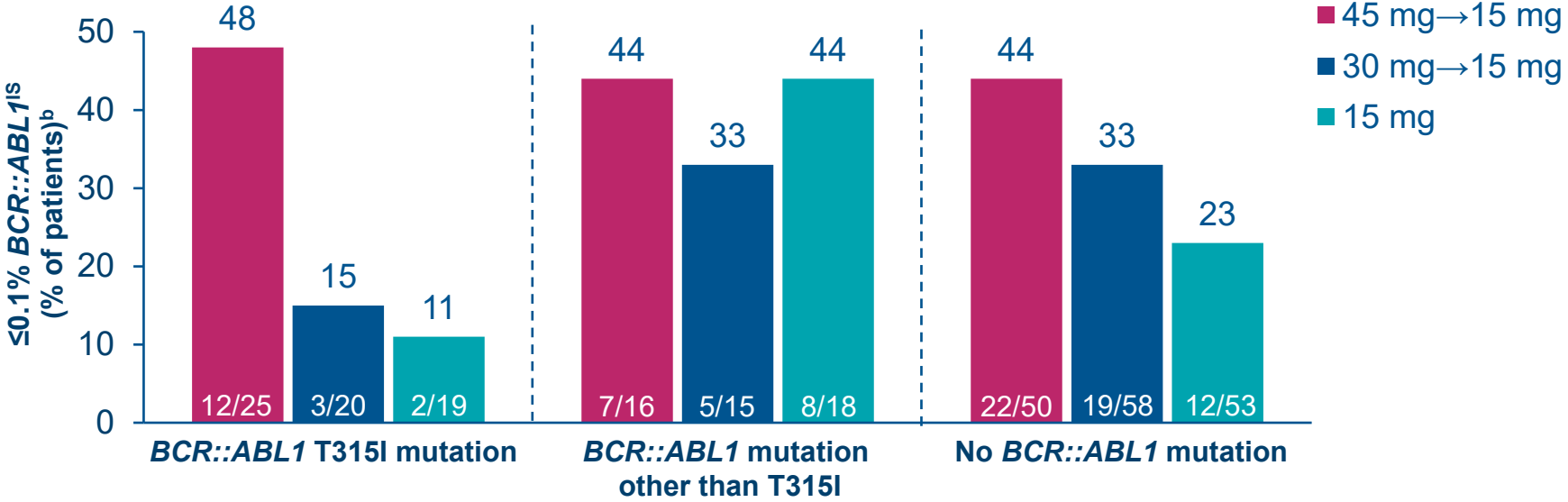
≤1% *BCR::ABL*^{IS} response rates by baseline mutation status by 48 months[a]



- ≤1% *BCR::ABL1*^{IS} (MR2) response rate by 48 months was highest in the 45-mg cohort
- The difference in response between dosing cohorts was highest for patients with T315I

[a]Analysis conducted in the ITT population; [b]Number of patients with ≤1% *BCR::ABL1*^{IS} is counted on cumulative basis by each time point, and a patient with response is counted only once. Percentages are based on the number of patients in each cohort as denominator.
ITT, intent-to-treat

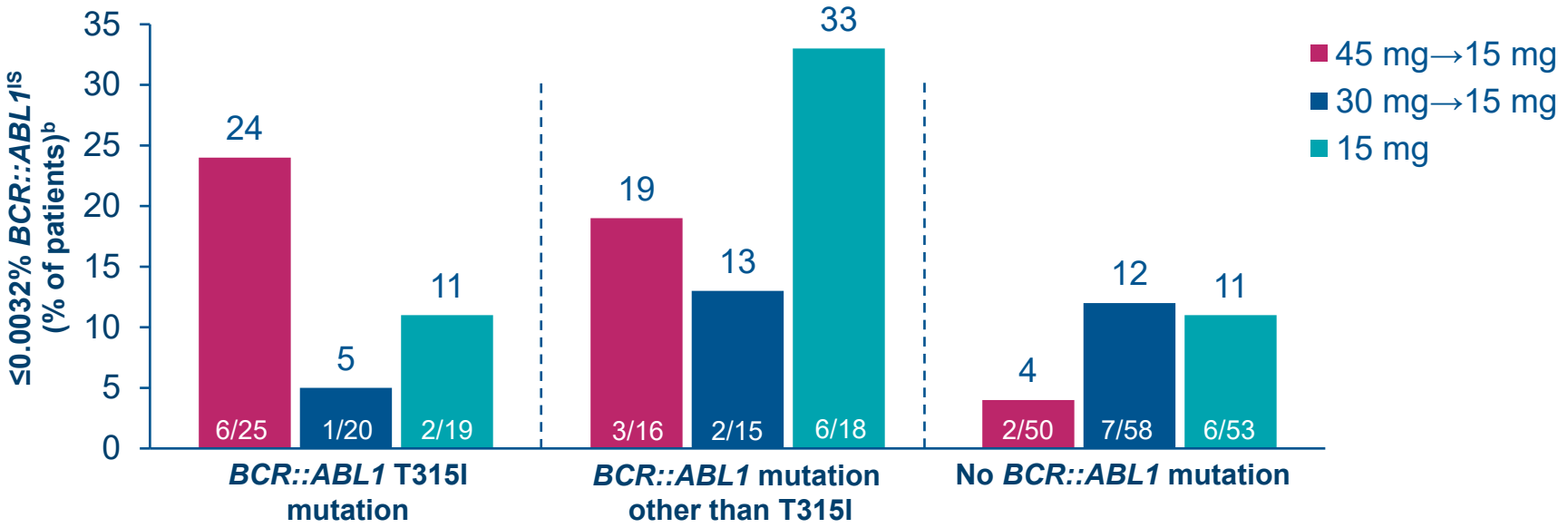
≤0.1% *BCR::ABL*^{IS} response rates by baseline mutation status by 48 months[a]



- ≤0.1% *BCR::ABL1*^{IS} (MR3) response rate by 48 months for the 45-mg cohort was highest in patients with the T315I mutation
- The difference in response between dosing cohorts was highest for patients with T315I

[a]Analysis conducted in the ITT population; [b]Number of patients with ≤0.1% *BCR::ABL1*^{IS} is counted on cumulative basis by each time point, and a patient with response is counted only once. Percentages are based on the number of patients in each cohort as denominator.

≤0.0032% *BCR::ABL*^{IS} response rates by baseline mutation status by 48 months[a]



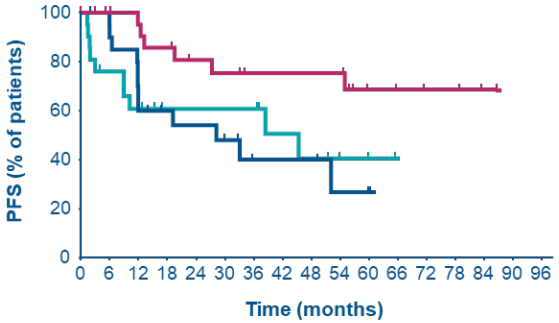
- ≤0.0032% *BCR::ABL1*^{IS} (MR4.5) response rate by 48 months was highest in patients with the T315I mutation for the 45-mg cohort

[a]Analysis conducted in the ITT population; [b]Number of patients with ≤0.0032% *BCR::ABL1*^{IS} is counted on cumulative basis by each time point, and a patient with response is counted only once. Percentages are based on the number of patients in each cohort as denominator.

PFS by mutation status and dosing cohort

BCR::ABL1 T315I mutation

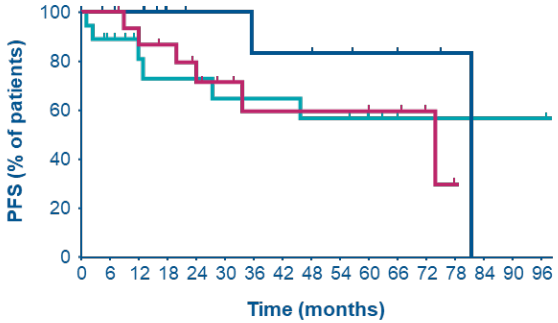
	No. (%) of patients with events	Median PFS, months (95% CI)	4-year PFS, % (95% CI)
45 mg→15 mg (n=25)	6 (24)	NE (55.2–NE)	75 (50–89)
30 mg→15 mg (n=21)	12 (57)	28.4 (12.0–NE)	40 (17–62)
15 mg (n=21)	10 (48)	45.6 (9.0–NE)	41 (15–65)



No. at risk															
45 mg→15 mg	25	22	20	18	15	14	12	12	12	12	7	6	3	3	1	0
30 mg→15 mg	21	20	14	10	9	8	4	4	4	2	2	0				
15 mg	21	15	12	8	8	8	8	5	4	3	2	0				

BCR::ABL1 mutation other than T315I

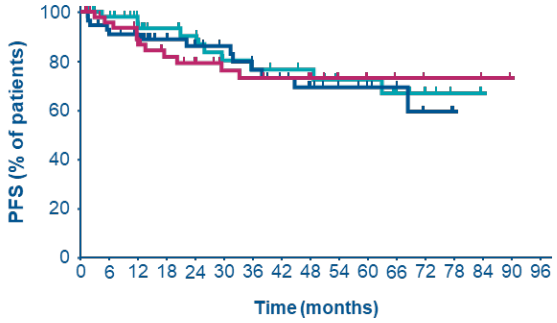
	No. (%) of patients with events	Median PFS, months (95% CI)	4-year PFS, % (95% CI)
45 mg→15 mg (n=16)	6 (38)	74.1 (19.9–NE)	60 (26–82)
30 mg→15 mg (n=15)	2 (13)	81.5 (35.6–NE)	83 (27–98)
15 mg (n=18)	6 (33)	NE (13.0–NE)	57 (27–78)



No. at risk															
45 mg→15 mg	16	16	14	12	10	7	5	5	5	5	5	4	2	1	0
30 mg→15 mg	15	13	12	7	6	6	5	5	5	4	3	3	2	1	1
15 mg	18	14	10	9	9	8	8	8	7	7	4	2	1	1	1	1	1

No *BCR::ABL1* mutation

	No. (%) of patients with events	Median PFS, months (95% CI)	4-year PFS, % (95% CI)
45 mg→15 mg (n=51)	11 (21)	NE (NE–NE)	73 (56–84)
30 mg→15 mg (n=58)	13 (22)	NE (68.8–NE)	69 (51–82)
15 mg (n=54)	10 (19)	NE (63.2–NE)	77 (58–88)



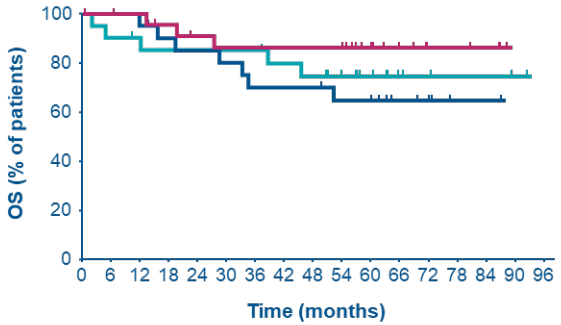
No. at risk															
45 mg→15 mg	51	44	39	32	30	25	24	23	21	17	12	8	6	2	2	1	0
30 mg→15 mg	58	49	46	34	31	27	23	20	17	12	10	8	5	3	0		
15 mg	54	50	42	32	29	24	21	20	19	16	13	11	7	2	1		

- In the 45-mg cohort, median PFS was not reached in patients with the T315I mutation or those with no *BCR::ABL1* mutation

OS by mutation status and dosing cohort

BCR::ABL1 T315I mutation

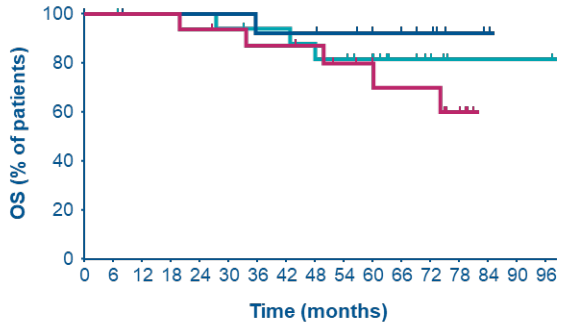
	No. (%) of patients with events	Median OS, months (95% CI)	4-year OS, % (95% CI)
45 mg→15 mg (n=25)	3 (12)	NE (NE–NE)	86 (63–95)
30 mg→15 mg (n=21)	7 (33)	NE (34.6–NE)	70 (45–85)
15 mg (n=21)	5 (24)	NE (45.6–NE)	75 (50–89)



No. at risk																
45 mg→15 mg	25	24	23	21	19	18	18	18	18	18	12	8	5	5	4	0
30 mg→15 mg	21	21	20	18	17	16	14	14	14	11	11	5	4	1	1	0
15 mg	21	19	18	17	17	17	17	15	14	12	8	4	3	2	2	1	0

BCR::ABL1 mutation other than T315I

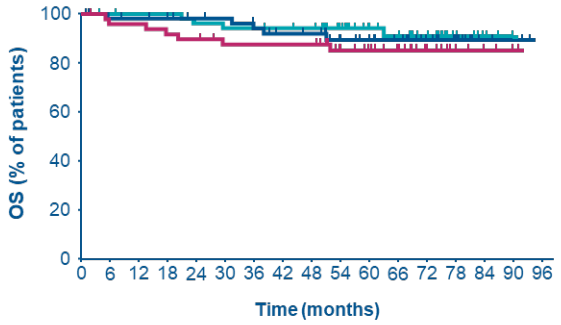
	No. (%) of patients with events	Median OS, months (95% CI)	4-year OS, % (95% CI)
45 mg→15 mg (n=16)	5 (31)	NE (49.8–NE)	87 (57–97)
30 mg→15 mg (n=15)	1 (7)	NE (NE–NE)	92 (57–99)
15 mg (n=18)	3 (17)	NE (NE–NE)	82 (53–94)



No. at risk																
45 mg→15 mg	16	16	16	16	15	14	13	13	12	10	9	7	7	4	0	
30 mg→15 mg	15	14	13	13	13	13	12	12	12	11	9	8	5	2	1	0
15 mg	18	18	17	17	17	16	15	15	14	13	10	6	4	1	1	1	1

No *BCR::ABL1* mutation

	No. (%) of patients with events	Median OS, months (95% CI)	4-year OS, % (95% CI)
45 mg→15 mg (n=51)	7 (14)	NE (NE–NE)	88 (75–94)
30 mg→15 mg (n=58)	5 (9)	NE (NE–NE)	92 (80–97)
15 mg (n=54)	4 (7)	NE (NE–NE)	94 (83–98)



No. at risk																
45 mg→15 mg	51	47	47	45	44	41	41	41	41	32	27	21	13	6	4	2	0
30 mg→15 mg	58	55	54	53	49	48	45	42	41	33	29	25	19	13	3	2	0
15 mg	54	53	52	52	49	48	48	47	46	39	30	27	21	10	4	1	0

- Median OS was not reached at the 4-year analysis regardless of mutation status across all dosing cohorts

Dose reductions and re-escalations after response or loss of response[a,b]

Characteristic	T315I mutation	
	45 mg→ 15 mg (n=25)	30 mg→15 mg (n=20)
Achieved ≤1% *BCR::ABL1*^{IS} at any time, n (%)	16 (64)	5 (25)
Dose reduced for efficacy, n (%)	15 (94)	5 (100)
Maintained response, n (%)	7 (47)	2 (40)
Loss of ≤1% *BCR::ABL1*^{IS} at any time, n (%)	9[c] (60)	3 (60)
Dose re-escalated after loss of response, n (%)	8 (89)	2 (67)
Regained ≤1% *BCR::ABL1*^{IS} after re-escalation		
Yes	6 (75)	1 (50)
No	2 (25)	1 (50)

[a]Includes all patients who had the first dose reduction to 15 mg occur after ≤1% *BCR::ABL1*^{IS} achieved; [b]ITT population; [c]One patient did not have dose a reduction to 15 mg upon achieving ≤1% *BCR::ABL1*^{IS}; this patient lost response after achieving ≤1% *BCR::ABL1*^{IS}.

- Of the patients who achieved response at any time but subsequently lost response, most regained ≤1% *BCR::ABL*^{IS} after dose re-escalation

Overview of TEAEs

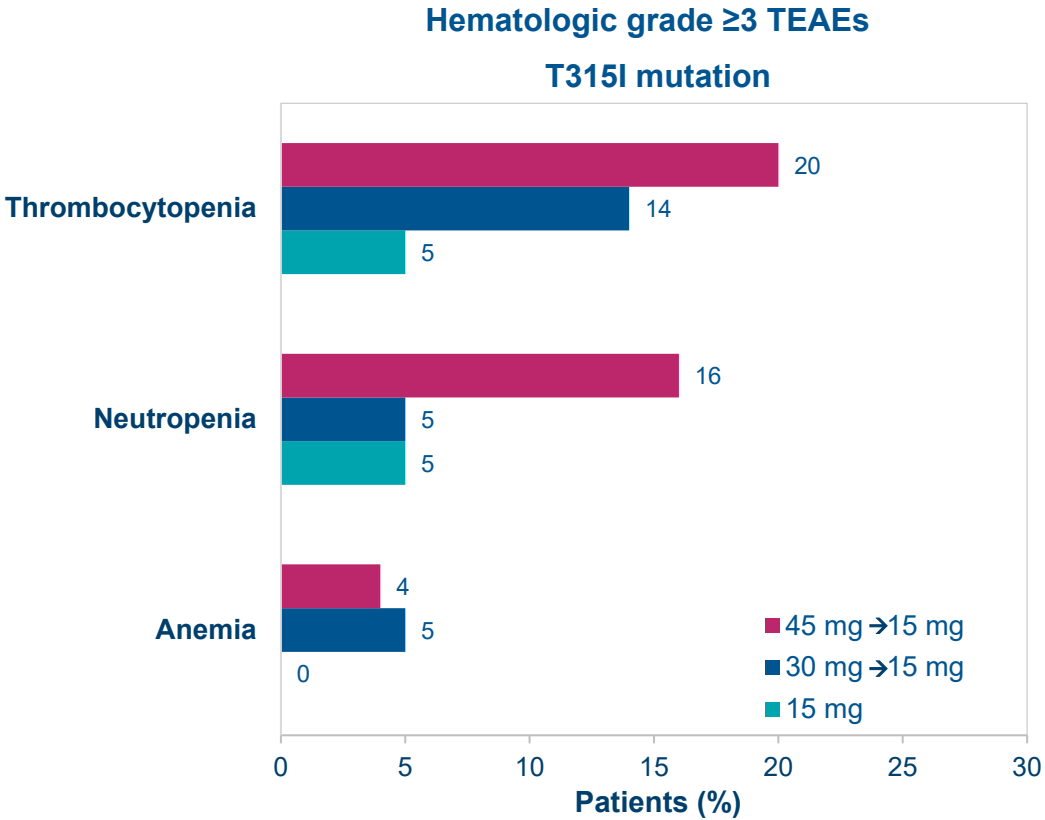
TEAEs	T315I mutation		
	45 mg→ 15 mg (n=25)	30 mg→ 15 mg (n=21)	15 mg (n=21)
TEAEs, n (%)			
Any TEAE	25 (100)	20 (95)	20 (95)
Grade 3–4	13 (52)	7 (33)	6 (29)
Serious	9 (36)	7 (33)	6 (29)
Grade 5[a]	2 (8)	1 (5)	2 (10)
Dose modification for TEAEs, n (%)			
Discontinuation[b]	2 (8)	3 (14)	1 (5)
Reduction	12 (48)	5 (24)	1 (5)
Interruption	16 (64)	10 (48)	8 (38)

[a]Includes deaths that occurred up to 30 days after the last ponatinib dose; [b]All TEAEs with "drug withdrawn" as the action taken

- The incidence of TEAEs was comparable across mutation status and dosing cohorts

TEAE, treatment-emergent adverse event.

Most common grade ≥3 TEAEs



- The most common hematologic grade ≥3 TEAEs were thrombocytopenia, neutropenia, anemia

Overview of TE-AOEs

TE-AOEs	T315I mutation		
	45 mg→ 15 mg (N=25)	30 mg→ 15 mg (N=21)	15 mg (N=21)
TE-AOEs, n (%)			
Any TE-AOE	2 (8)	3 (14)	1 (5)
Grade 3–4	1 (4)	3 (14)	1 (5)
Grade 5	0	0	0
Dose modifications, n (%)			
Discontinuation	0	1 (5)	0
Reduction	0	2 (10)	0
Interruption	1 (4)	2 (10)	1 (5)
Exposure-adjusted AOEs, patients with events/100 PY, % (95% CI)	2.37 (0.00–5.74)	7.32 (0.00–15.64)	2.83 (0.00–7.99)

- Rates of TE-AOEs were generally low across dosing cohorts regardless of mutation status, and there were no deaths due to TE-AOEs

TE-AOE, treatment-emergent arterial occlusive event; PY, patient years.

Conclusions

- These results from this post hoc analysis of the 4-year follow-up of the OPTIC study support ponatinib's long-term efficacy and manageable safety profile in patients with the difficult-to-treat T315I mutation
- Although this post hoc analysis had smaller numbers of patients in the mutation and dosing cohorts, these results in patients with CP-CML with the T315I mutation appear consistent with previous analyses of the OPTIC trial[1]
- Response-based dosing with ponatinib demonstrated long-term manageable safety, including a low rate of exposure-adjusted AOEs
- Observed responses were associated with robust long-term survival in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy with or without the T315I mutation

1. Cortes J, et al. Blood 2021;138:2042–50.

Acknowledgments

- We thank all the patients and their families, and the investigators and staff at all clinical sites, for their participation in the study

- Thank you for your time and attention!

For an e-Print, scan this QR code.